ORIGINAL REPORT

Impact of Age and Comorbidity on Non–Small-Cell Lung Cancer Treatment in Older Veterans

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A B S T R A C T

Purpose
Because comorbidity affects cancer treatment outcomes, guidelines recommend considering comorbidity when making treatment decisions in older patients with lung cancer. Yet, it is unclear whether treatment is targeted to healthier older adults who might reasonably benefit.

Patients and Methods
Receipt of first-line guideline-recommended treatment was assessed for 20,511 veterans age ≥ 65 years with non–small-cell lung cancer (NSCLC) in the Veterans Affairs (VA) Central Cancer Registry from 2003 to 2008. Patients were stratified by age (65 to 74, 75 to 84, ≥ 85 years), Charlson comorbidity index score (0, 1 to 3, ≥ 4), and American Joint Committee on Cancer stage (I to II, IIIA to IIIB, IIIB with malignant effusion to IV). Comorbidity and patient characteristics were obtained from VA claims and registry data. Multivariate analysis identified predictors of receipt of guideline-recommended treatment.

Results
In all, 51% of patients with local, 35% with regional, and 27% with metastatic disease received guideline-recommended treatment. Treatment rates decreased more with advancing age than with worsening comorbidity for all stages, such that older patients with no comorbidity had lower rates than younger patients with severe comorbidity. For example, 50% of patients with local disease age 75 to 84 years with no comorbidity received surgery compared with 57% of patients age 65 to 74 years with severe comorbidity ($P < .001$). In multivariate analysis, age and histology remained strong negative predictors of treatment for all stages, whereas comorbidity and nonclinical factors had a minor effect.

Conclusion
Advancing age is a much stronger negative predictor of treatment receipt among older veterans with NSCLC than comorbidity. Individualized decisions that go beyond age and include comorbidity are needed to better target NSCLC treatments to older patients who may reasonably benefit.

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INTRODUCTION

More than 70% of future lung cancer cases in the United States will occur in adults age ≥ 65 years,[1] with non–small-cell lung cancer (NSCLC) comprising the vast majority of cases.[2] Although NSCLC in older adults is often regarded as having a dismal prognosis, data suggest that treatment of NSCLC improves survival even for the elderly. In localized NSCLC, retrospective studies have shown improved survival for healthy octogenarians receiving surgery.[3-6] In trials on locoregional NSCLC, patients age ≥ 70 years gain survival benefit similar to those of their younger counterparts with adjuvant chemotherapy for resectable disease and combined chemoradiotherapy for unresectable disease.[7-11] Even in trials of metastatic NSCLC, patients age ≥ 70 years benefit from chemotherapy with improved overall survival and quality of life (QOL) compared with best supportive care.[12-18] Yet elderly patients who enroll onto trials generally have few comorbidities and are not representative of the heterogeneous real-world older population with NSCLC.

Comorbidity can have an impact on care for patients with NSCLC in a variety of ways. First, patients with comorbidity are more likely to experience treatment toxicity, and treatments may exacerbate underlying comorbidity.[19-21] Second, comorbidity decreases the likelihood of completing treatment. In a large trial,[22] patients with advanced NSCLC who had Charlson comorbidity index (CCI) scores ≥ 2 were more likely to discontinue chemotherapy. Third, significant comorbidities can limit life expectancy, particularly in earlier-stage cancers, decreasing the potential survival benefit of cancer treatment.[23,24] Large trials in locoregional
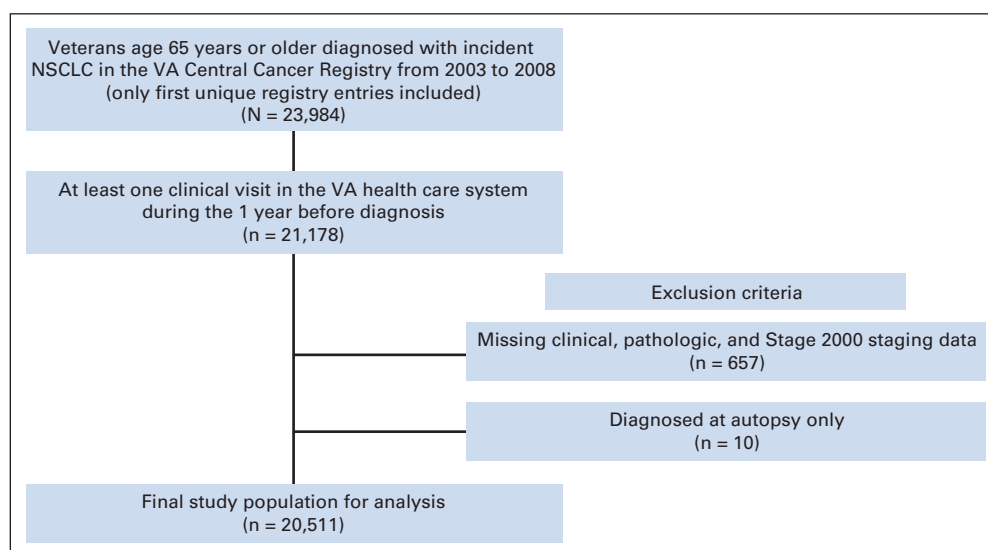
Fig 1. Exclusions used to define the final cohort of older veterans with non–small-cell lung cancer (NSCLC) in the Veterans Affairs (VA) Central Cancer Registry.

NSCLC[25,26] have shown that increased CCI score was associated with worse survival, whereas age was not prognostic. Accordingly, National Comprehensive Cancer Network (NCCN) guidelines advise physicians to consider comorbidity when recommending cancer treatment to older patients.[27]

However, it is unclear to what extent NSCLC treatment is targeted to healthy older adults who might reasonably benefit. Many studies of elders with NSCLC did not include comorbidity; those that did used data before 2003,[28-32] before the influx of data supporting NSCLC treatment in the fit elderly,[3-18] and before the introduction of less toxic treatments, including tyrosine kinase inhibitors.[33-36] Moreover, many prior NSCLC population studies did not evaluate the simultaneous impact of age and comorbidity on NSCLC treatment. Therefore, we conducted this large national study to determine receipt of cancer treatment among veterans age $\geq$ 65 years diagnosed with NSCLC stratified by age, comorbidity, and stage.

PATIENTS AND METHODS

Data Sources and Patients

We identified a cohort of patients age $\geq$ 65 years diagnosed with NSCLC within the Veterans Affairs (VA) health care system between January 1, 2003, and December 31, 2008, and determined rates of guideline-recommended NSCLC treatment. Data for this study were obtained from the VA Central Cancer Registry (VACCR) and the Veterans Health Administration National Patient Care Database. The VACCR is administered by the VA Chief Program Office and aggregates data from 132 VA medical centers with tumor registries. Data are uniformly collected on all patients who received a cancer diagnosis or received their first-line cancer treatment at a VA medical center. Registry staff use standard protocols, including those commissioned by the American College of Surgeons,[37] to document demographic and tumor characteristics and primary treatment provided within the VA system and at non-VA facilities. An external audit of the VACCR found that its case capture rate was comparable to Surveillance, Epidemiology, and End Results (SEER) data from 2002 onward.[38] The centralized Veterans Health Administration National Patient Care Database captures all inpatient and outpatient claims within the VA.

These sources generated a cohort of 21,178 patients age $\geq$ 65 years diagnosed with NSCLC between 2003 and 2008, with at least one visit to the VA health care system in the year before diagnosis. NSCLC cases were identified from the VACCR by using bronchus and lung (International Classifica-

tion of Diseases for Oncology, Third Edition [ICD-O-3]) primary site codes C34.0-C34.3 and C34.8-C34.9.[39] Only NSCLC ICD-O-3 histology codes were included: adenocarcinoma, bronchioloalveolar carcinoma, squamous cell carcinoma, carcinoma not otherwise specified, and other variants. Only the first unique NSCLC diagnosis in the VACCR for each patient was included. We excluded 657 patients (3%) without staging information and 10 patients diagnosed with NSCLC at autopsy. This resulted in our final analytic cohort of 20,511 elderly veterans with NSCLC (Fig 1).

Data Collection and Measurement

The main outcome was receipt of first-line guideline-recommended treatment based on NCCN[40] guidelines. First-line treatment was defined as treatments received within 6 months from diagnosis. Since NCCN guidelines recommend treatments based on stage at presentation, we stratified patients into three categories: local disease (stage I to II), regional disease (stage IIIA to IIIB without malignant effusion), or metastatic disease (stage IIIB with malignant effusion to IV). The VACCR staged patients according to the American Joint Committee on Cancer (AJCC) Sixth Edition staging guidelines.[41] Clinical staging information was used when available (91% of patients); when clinical staging information was missing, pathologic staging or SEER Summary Stage 2000[42] was substituted (9% of patients).

For local NSCLC, guidelines recommend resection for attempt at cure.[43] For the fit elderly, including octogenarians, this is based on retrospective studies in localized disease showing survival benefit even with limited thoracic resections.[3-6] Therefore, for patients with local disease, our primary outcome was receipt of surgery (alone or with other treatment modalities), ranging from wedge resection to pneumonectomy. For patients who did not receive surgery, we described rates of other treatment, defined as radiation and/or chemotherapy, and rates of no treatment.

For regional NSCLC, guidelines recommend surgery and chemotherapy, with or without radiation for resectable disease and chemotherapy plus radiation for unresectable disease.[44,45] For the fit elderly, this is based on retrospective analyses in regional NSCLC showing that patients age $\geq$ 70 years had similar survival benefit compared with patients younger than age 70 years when receiving adjuvant chemotherapy for resectable disease and chemoradiotherapy for unresectable disease, albeit with increased toxicity.[7-11] Therefore, for patients with regional disease, our primary outcome was receipt of surgery or chemotherapy plus radiation. For patients who did not receive these treatments, we described rates of other treatment, defined as chemotherapy or radiation alone, and rates of no treatment.

For metastatic disease, guidelines recommend chemotherapy to improve survival and QOL.[46,47] For the elderly, this is based on prospective trials, in which single-agent chemotherapy showed survival benefit for patients age 70 to 86 years.[12-14] Regarding doublet therapy, retrospective analyses have shown

Table 1. Characteristics of Veterans Age ≥ 65 Years With NSCLC by Stage at Presentation (N = 20,511)

Characteristic	Local Disease (n = 6,986; 34%)		Regional Disease (n = 4,635; 23%)		Metastatic Disease (n = 8,890; 43%)	
	No.	%	No.	%	No.	%
Age at diagnosis, years*						
65-74	3,569	51	2,288	49	4,408	50
75-84	3,040	44	2,065	45	3,832	43
≥ 85	377	5	282	6	650	7
Charlson comorbidity index*						
0	1,130	16	871	19	1,865	21
1-3	4,448	64	2,959	64	5,456	61
≥ 4	1,408	20	805	17	1,569	18
Selected Charlson comorbid conditions						
Chronic pulmonary disease	3,945	56	2,468	53	4,333	49
Diabetes with and without complications	1,803	26	1,163	25	2,264	25
Non-lung malignancy	1,631	23	872	19	1,767	20
Peripheral vascular disease	1,365	20	834	18	1,532	17
Congestive heart failure	845	12	599	13	1,179	13
Cerebrovascular disease	879	13	588	13	1,120	13
Moderate or severe renal disease	587	8	353	8	684	8
Myocardial infarct	425	6	260	6	485	5
Dementia	90	1	76	2	164	2
Sex						
Male	6,884	99	4,591	99	8,780	99
Female	102	1	44	1	110	1
Race/ethnicity*						
White	5,931	85	3,798	82	7,267	82
Black	913	13	757	16	1,439	16
Other	142	2	80	2	184	2
Married*†						
Yes	3,974	57	2,550	55	4,674	53
No	2,996	43	2,078	45	4,203	47
Lived in ZCTA in which ≥ 25% of adults had a college education†‡						
Yes	1,725	25	1,136	25	2,168	24
No	5,042	72	3,347	72	6,444	72
Median annual income in ZCTA†‡						
Highest tertile	2,285	33	1,451	31	2,831	32
Middle tertile	2,339	33	1,550	33	2,865	32
Lowest tertile	2,144	31	1,484	32	2,921	33
Insurance status§						
Veterans Affairs/military	4,646	67	3,113	67	6,137	69
Medicare/Medicaid	2,184	31	1,421	31	2,595	29
Private	47	1	35	1	67	1
Other	109	2	66	1	91	1
Geographic region¶						
South	3,131	45	2,171	47	4,093	46
Midwest	1,518	22	966	21	1,903	21
West	1,384	20	827	18	1,611	18
Northeast	953	14	671	14	1,283	14
Level of urbanization†‖						
Urban	4,771	69	3,177	69	6,070	69
Rural	2,163	31	1,414	31	2,711	31
Year of diagnosis						
2003-2005	3,404	49	2,359	51	4,377	49
2006-2008	3,582	51	2,276	49	4,513	51
Tumor histology*						
Adenocarcinoma	1,923	28	957	21	2,591	29
Bronchioloalveolar carcinoma	269	4	66	1	104	1
Squamous cell carcinoma	2,741	39	1,911	41	2,247	25
Other non–small-cell variants#	270	4	148	3	282	3
Carcinoma, not otherwise specified	1,783	26	1,553	34	3,666	41

(continued on following page)

	Local Disease (n = 6,986; 34%)		Regional Disease (n = 4,635; 23%)		Metastatic Disease (n = 8,890; 43%)	
Characteristic	No.	%	No.	%	No.	%
Tobacco history*†						
Current smoker	2,699	39	1,991	43	3,680	41
Former smoker	3,379	48	2,122	46	4,118	46
Never used	355	5	206	4	434	5

Table 1. Characteristics of Veterans Age ≥ 65 Years With NSCLC by Stage At Presentation (N = 20,511) (continued)

Abbreviations: NSCLC, non–small-cell lung cancer; ZCTA, ZIP code tabulation area.

*Characteristics of age, comorbidity, race, marital status, tumor histology, and tobacco history differed across patients with local, regional, or metastatic disease ($P < .001$) using the χ^2 test.

†Only the following five variables had any missing data: tobacco history (n = 1,527; 7.4%); ZCTA income level (n = 641; 3.1%); ZCTA education level (n = 649; 3.2%); level of urbanization (n = 205; 1%); married (n = 36; 0.2%).

‡Veterans Affairs (VA) data and linkage to the 2000 US Census on the basis of each patient's ZIP code at the time of diagnosis was used to determine the proportion of adults with a college education and median annual income divided into tertiles.

§Insurance status was stratified into VA and active military insurance, Medicare/Medicaid, private insurance, and other.

¶Veterans Integrated Service Networks were categorized geographically into four regions defined by the US Census Bureau.[52]

‖To determine level of urbanization, ZIP codes were linked to rural-urban commuting areas codes and dichotomized into urban or rural.[53-55]

#Other non–small-cell variants include large-cell carcinoma, large-cell neuroendocrine carcinoma, and sarcomatoid carcinoma.

that patients age 70 to 80 years have similar survival benefit compared with those younger than age 70 years, but potentially inferior outcomes for those older than age 80 years.[15-17] Therefore, for patients with metastatic disease, our primary outcome was receipt of chemotherapy, which included cytotoxic and targeted drugs, including tyrosine kinase inhibitors, in both single- and multiagent regimens. For patients who did not receive chemotherapy, we described rates of other treatment, defined as radiation or surgery, and rates of no treatment.

Predictor Variables

The two main predictors were age and comorbidity as measured by the CCI.[48] Age was categorized into three groups: 65 to 74 years, 75 to 84 years, and ≥ 85 years. The CCI, which incorporates 19 chronic diseases weighted according to their association with mortality, was calculated for each patient by using VA inpatient and outpatient claims data during the year before diagnosis, via the Deyo et al[49] adaptation of the CCI for administrative databases. Because NSCLC is the disease of interest (rather than a comorbidity), lung cancer and metastatic tumor codes were excluded from the CCI for all patients. We categorized patients as having no comorbidity if their CCI was 0, average comorbidity if their CCI was 1 to 3, and severe comorbidity if their CCI was ≥ 4. We chose these cutoffs a priori to assess how extremes in comorbidity influence receipt of NSCLC treatment; such cutoffs have been used in previous studies.[50] Additional variables thought to influence receipt of NSCLC treatment were also determined from VA data and linkage to the 2000 US Census.[51-55] The Committee on Human Research at the University of California at San Francisco and the Research and Development Committee at the San Francisco VA Medical Center approved this study.

Statistical Analysis

We computed the percentages of veterans who received guideline-recommended treatment according to baseline characteristics stratified by stage. To characterize the association between baseline characteristics and receipt of guideline-recommended treatment, adjusted treatment rates were derived from a logistic regression model that controlled for all baseline covariates. Adjusted treatment rates were calculated by fixing all but the covariate of interest at their mean values. Covariates included age, CCI, sex, race/ethnicity, marital status, ZIP code tabulation area (ZCTA), education level, median income, insurance status, geographic region, level of urbanization, year of diagnosis, tumor histology, and tobacco use history. Chronic obstructive pulmonary disease was not included in the multivariate analysis given that it is part of the CCI score. Only five covariates had any missing data, which were treated as dummy variables in the logistic regression analysis (Table 1). All analyses were conducted by using SAS 9.2 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

Baseline characteristics of the 20,511 elderly veterans with NSCLC in our cohort are provided in Table 1. At presentation, 6,986 patients (34%) had local disease, 4,635 (23%) had regional disease, and 8,890 (43%) had metastatic disease. Median age was 74 years (interquartile range, 70 to 79 years). Median CCI was 2 (interquartile range, 1 to 3), with scores ranging from 0 to 13. In all, 19% of patients (3,866) had no comorbidity, 63% (12,863) had average comorbidity, and 18% (3,782) had severe comorbidity. The most prevalent comorbid illness was chronic obstructive pulmonary disease (52%), followed by diabetes (26%), non–lung malignancies (21%), and peripheral vascular disease (20%). NSCLC stage groups differed in age, comorbidity, race, marital status, tumor histology, and tobacco use history ($P < .001$).

Rates of NSCLC Treatment

Guideline-recommended treatment was received by 51% of patients (3,549 of 6,986) with local disease, 35% of patients (1,599 of 4,635) with regional disease, and 28% of patients (2,464 of 8,890) with metastatic disease. Characteristics associated with receipt of guideline-recommended treatment are listed in Table 2 according to stage. Age was the strongest predictor of receipt of guideline-recommended treatment regardless of stage. The percentage of patients with local disease who received surgery decreased markedly with advancing age, from 61% for patients age 65 to 74 years to 44% for patients age 75 to 84 years to 18% for patients age ≥ 85 years ($P < .001$), a 30% and 70% decrease, respectively. Similarly, in metastatic disease, rates of chemotherapy declined from 34% for patients age 65 to 74 years to 23% for patients age 75 to 84 years to 10% for patients ≥ 85 ($P < .001$), 30% and 70% decreases, respectively. In contrast, worsening comorbidity was associated with a small decrease in the rate of guideline-recommended treatment for all stages. Among patients with local disease, receipt of surgery ranged from 59% for patients with no comorbidity to 46% for patients with severe comorbidity ($P < .001$), a 20% decrease. In metastatic disease, patients with no comorbidity had

Table 2. Rates of Guideline-Recommended Treatment in Veterans Age ≥ 65 Years With NSCLC by Stage and Patient Characteristics

Characteristic	Local Disease (n = 6,986)		Regional Disease (n = 4,635		Metastatic Disease (n = 8,890)	
	Unadjusted Treatment Rate (%)*	Adjusted Treatment Rate (%)*	Unadjusted Treatment Rate (%)†	Adjusted Treatment Rate (%)†	Unadjusted Treatment Rate (%)‡	Adjusted Treatment Rate (%)‡
Age at diagnosis, years						
65-74	60.5	59.8	44.4	44.7	34.3	34.3
75-84	43.5§	43.1§	26.3§	25.9§	23.1§	22§
≥ 85	18.3§	18.5§	14.5§	14§	10.2§	9.3§
Charlson comorbidity index						
0	58.8	60	39	38.7	29.7	27.6
1-3	50.3§	48.9§	34.8	33.7	28.3	26.9
≥4	45.9§	45.7§	28.3§	27.8§	23.2§	22.4§
COPD¶						
Yes	46.4	46.2	32.4	31.7	26.8	26.1
No	56.5§	55.1§	36.9	35.5	28.6	26.8
Sex						
Male	50.7	50.1	34.6	33.7	27.7	26.1
Female	55.9	52.1	20.5	22.1	31.8	33.1
Race/ethnicity						
White	51.9	51.1	35.5	34	28.1	26.2
Black	44.4§	43.7§	30	31.1	25.6	26.3
Other	47.2	49.9	28.8	34.4	29.9	26.4
Married						
Yes	52.9	52.3	36.4	35.3	30.5	29.1
No	48§	47.2§	32.3	31.4	24.6§	23.3§
Lived in ZCTA in which ≥ 25% of adults had a college education						
Yes	50	49.1	34.2	33.6	27.4	25.8
No	53	52.8	35.7	33.5	28.5	27.5
Median annual income of ZCTA						
Highest tertile	53.3	52.2	37.1	37.2	28.6	27.3
Middle tertile	52	51.9	36.1	34.5	27.7	26.5
Lowest tertile	46.7§	45.9	30.6§	29.2§	26.6	24.9
Insurance status						
Veterans Affairs/military	50.7	49.8	33.7	32.8	27.5	26
Medicare/Medicaid	51	50.5	36	34.9	27.7	26.1
Private	57.4	54	34.3	29	41.8	40.5
Other	50.5	50.8	40.9	40.5	35.2	32.2
Geographic region						
South	51.2	50.7	33.9	33.7	28.1	26.3
Midwest	45.7§	42.5§	35.3	33	27.1	25.4
West	50.6	51.9	32.8	31.1	28	26.9
Northeast	58.1§	57.5	37.4	37	27.2	26.3
Level of urbanization						
Urban	51.3	52.5	35.9	35.2	28.4	27.2
Rural	50.7	49	34.1	32.8	27	25.8
Year of diagnosis						
2003-2005	51.5	51.3	34	33.3	25.9	24.3
2006-2008	50.1	48.9	35	33.8	29.5§	28.2§
Tumor histology						
Adenocarcinoma	67.7	67.6	37.7	36.8	33.6	31.7
Bronchioloalveolar carcinoma	79.6§	80.2§	39.4	39.6	44.2	42.1
Squamous cell carcinoma	54.3§	54.2§	38.6	37.4	31.6	30.2
Other non–small-cell variants	74.1	73.8	46.6	44.8	23.8§	22.1
Carcinoma, NOS	19.3§	19.6§	26.1§	26.1§	21§	20.6§
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Table 2. Rates of Guideline-Recommended Treatment in Veterans Age ≥ 65 Years With NSCLC by Stage and Patient Characteristics (continued)

Characteristic	Local Disease (n = 6,986)		Regional Disease (n = 4,635		Metastatic Disease (n = 8,890)	
	Unadjusted Treatment Rate (%)*	Adjusted Treatment Rate (%)*	Unadjusted Treatment Rate (%)†	Adjusted Treatment Rate (%)†	Unadjusted Treatment Rate (%)‡	Adjusted Treatment Rate (%)‡
Tobacco history						
Current smoker	50.2	47.3	33.7	30.7	26.5	23.4
Former smoker	52.5	52.6§	37	37.3§	29.4	28.5§
Never used	47.3	46.8	23.8	24.7	28.8	30

Abbreviations: COPD, chronic obstructive pulmonary disease; NOS, not otherwise specified; NSCLC, non–small-cell lung cancer; ZCTA, ZIP code tabulation area.
*Surgery.
†Surgery or chemotherapy plus radiation.
‡Chemotherapy.
§Differences were tested by *t* test of the regression parameters test where the reference category is the first-listed category for each of the above multinomial variables. Differences with *P* < .001 are indicated by the § symbol.
¶Multivariate analysis included all covariates in this table, except for COPD given that it is part of the Charlson comorbidity index score.

chemotherapy rates of 30% compared with 23% for those with severe comorbidity (*P* < .001), a 20% decrease.

We also examined the simultaneous impact of age and comorbidity on treatment rates. We found that older patients with no comorbidity generally had lower rates of guideline-recommended treatment than younger patients with severe comorbidity across all stages (Fig 2). Among those with local disease, 50% of patients age 75 to 84 years with no comorbidity received surgery compared with 57% of patients age 65 to 74 years with severe comorbidity (*P* < .001; Fig 2). When we expanded treatment to include both guideline-recommended and other treatments, treatment rates still declined most strongly with age. Among those with local disease, 70% of patients age 75 to 84 years with no comorbidity received any treatment compared with 82% of patients age 65 to 74 years with severe comorbidity (*P* < .001; Fig 2).

In multivariate analysis, adjusted rates of guideline-recommended treatment across all stages were similar to unadjusted rates. Age had the strongest negative independent effect on guideline-recommended treatment regardless of stage (Table 2). Comorbidity had a weaker negative independent effect. Other independent predictors of treatment across all NSCLC stages included histology and tobacco use history (*P* < .001; Table 2).

DISCUSSION

This large population-based study of veterans age ≥ 65 years provides the most recent real-world data on the simultaneous impact of age and comorbidity on receipt of treatment across all stages of NSCLC. We found that treatment rates of elderly veterans diagnosed with NSCLC during 2003 to 2008 remained similar to those from population-based studies before 2003.[28,29] Advancing age was strongly and inversely predictive of NSCLC treatment rates, whereas comorbidity was a weak negative predictor across all stages, such that rates of guideline-recommended treatment dropped by more than two thirds for those age ≥ 85 years compared with those younger than age 75 years, but by less than a quarter for those with no comorbidity compared with those with severe comorbidity. Looking at age and comorbidity simultaneously, younger patients with severe comorbidity had higher rates of guideline-recommended treatment than older patients with no co-

morbidity regardless of NSCLC stage. As a result, many healthier older adults with NSCLC are not receiving guideline-recommended treatment, although relatively younger adults with severe comorbidity are aggressively treated.

In the last decade, there has been an influx of data that support providing NSCLC treatment to fit elders, ranging from retrospective analyses to prospective elderly-specific clinical trials.[3-18] Yet, treatment rates in our study for 2003 to 2008 are similar to those from earlier studies. In localized NSCLC, a Southern Netherlands registry study from 1995 to 1999[29] showed surgical rates ranging from 61% to 79% for patients age 60 to 79 years and 9% for those age ≥ 80 years. In our study, 60% of patients age 65 to 74 years with localized disease and 15% of patients age ≥ 85 years received surgery. Among patients with metastatic NSCLC, a SEER-Medicare study from 1997 to 2002 showed 34% of patients age 65 to 74 years and 13% of patients age ≥ 85 years received chemotherapy.[28] In our study, among patients with metastatic disease, 34% of patients age 65 to 74 years and 10% of patients age ≥ 85 years received chemotherapy. Therefore, despite increasing data showing survival benefit and acceptable toxicity of treatment for adults older than age 65 years, treatment rates in the elderly have not increased much over the past decade.

Our study also found that age was a stronger negative predictor for receipt of guideline-recommended treatment than comorbidity across all stages, despite evidence and guidelines that stress the importance of assessing comorbidity. In addition, with the exception of age and tumor histology, all other factors evaluated in this study had only a small effect on receipt of guideline-recommended treatment, as evidenced by the similarity between adjusted and unadjusted rates. Even when expanding treatment to include both guideline-recommended and other treatments, we found that for all stages, age remained a stronger negative predictor than comorbidity for receipt of any cancer treatment.

When age and comorbidity are considered together, we observed that older patients with no comorbidity were treated at lower rates than relatively younger patients with severe comorbidity. This is despite large trials in locoregional NSCLC showing that increased CCI was associated with worse survival whereas age was not prognostic.[25,26] Although we did not have data on performance status (PS), which has been shown to be independent of comorbidity in patients
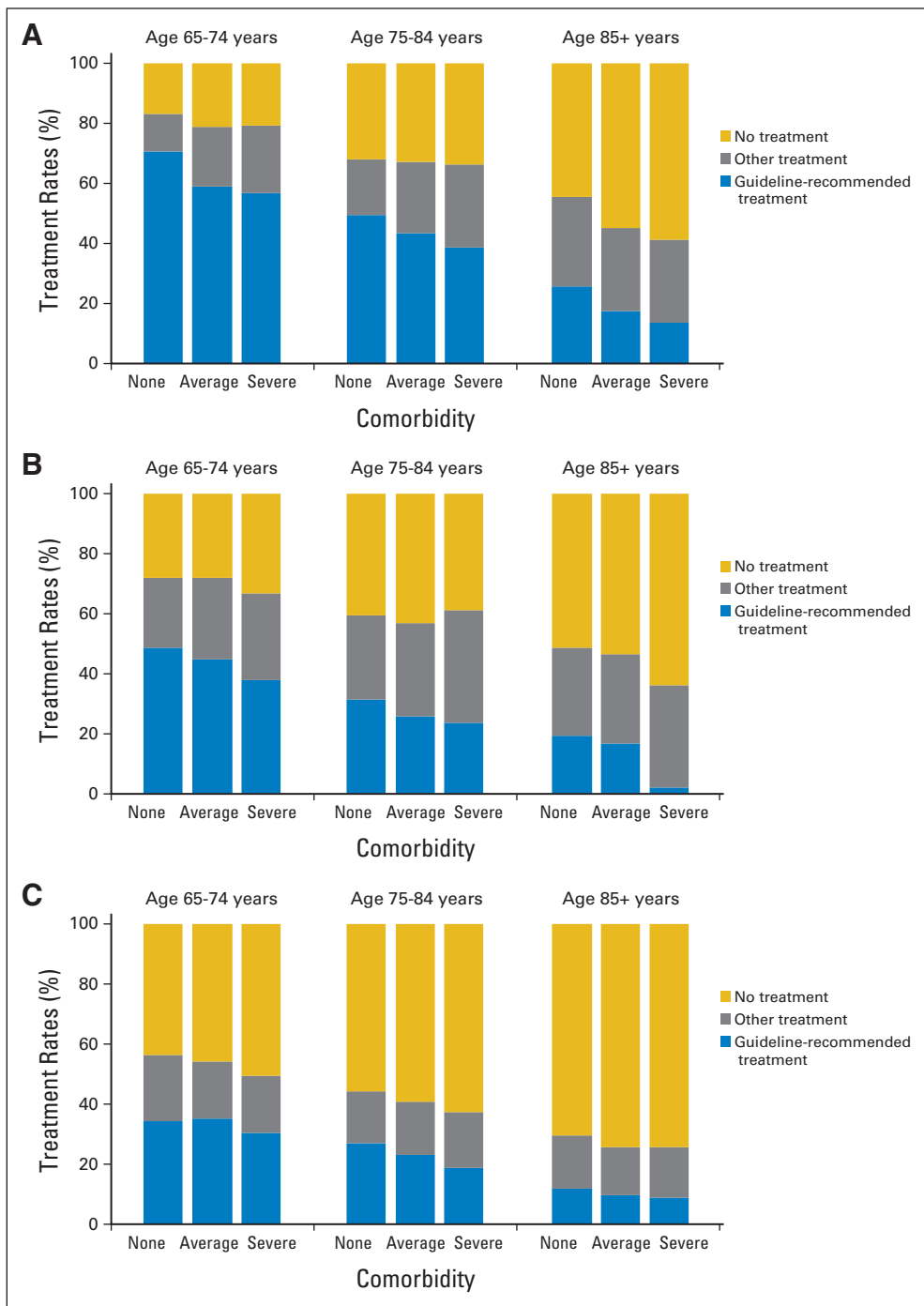
Fig 2. (A) Local disease: Other treatment (gray) includes radiation and/or chemotherapy, and guideline-recommended treatment (blue) includes surgery. (B) Regional disease: Other treatment (gray) includes chemotherapy or radiation alone, and guideline-recommended treatment (blue) includes surgery or chemotherapy plus radiation. (C) Metastatic disease: Other treatment (gray) includes surgery or radiation, and guideline-recommended treatment (blue) includes chemotherapy.

with cancer,[56] it is unlikely that the disparity in treatment rates between older patients with no comorbidity and their younger counterparts with severe comorbidity can be entirely explained by poor PS alone. Rather, chronologic age has been shown to dominate cancer screening decisions in older adults regardless of health status,[50] as well as treatment decisions in other types of cancers,[57] and our findings suggest this is also true for NSCLC treatment decisions.

There are several possible explanations for why NSCLC treatment is not optimally targeted to older patients with no or few comorbidities. First, healthy older patients may refuse treatment or not get referred to specialists, because they and their physicians may view lung cancer as a disease with dismal prognosis for which treatment is futile. For example, in a survey of patients with early-stage NSCLC conducted in 2005 to 2008, patients' own negative perceptions of prognosis significantly predicted lower rates of surgery.[58] Studies of other cancer types have shown that older patients are referred to cancer specialists at lower rates compared with younger patients.[59,60]

Second, without a standardized method for evaluating comorbidity in clinical practice, physicians may not rigorously evaluate comorbidity. Currently, there are several different comorbidity scales

(Adult Comorbidity Evaluation-27 [ACE-27], CCI, and Cumulative Illness Rating Scale for Geriatrics [CIRS-G])[56] with no consensus on the best method for targeting cancer treatment to older adults who will benefit and limit it in those at substantial risk for treatment toxicity. Hurria et al[61] recently published data on a new tool incorporating comorbidity with tumor and host characteristics into a risk score that predicts chemotherapy toxicity in older patients better than traditional PS measures. Our study supports the need for such instruments that include comorbidity.

Our study has several limitations. First, comorbidity scores based on administrative data may underestimate comorbidity. Although it was not possible in prior studies, for this study we were able to obtain comorbidity codes from both outpatient and inpatient sources under an integrated electronic health care system, and we used the validated CCI. Second, our study lacked an assessment of PS and functional status (activities of daily living and instrumental activities of daily living). To partially address this, we chose a comorbidity threshold that was severe (CCI $\geq$ 4), which likely would have an impact on a patient's PS and functional status. Third, we lacked detailed data on severity of comorbidity, such as forced expiratory volume at one second and diffusing capacity of lungs for carbon monoxide data, which are important for treatment decision making. Fourth, the VACCR did not collect data on type of radiation treatment modality or QOL outcomes. Fifth, we excluded a small percentage (3%) of patients with no staging information. As a result, we may slightly overestimate treatment rates, because some elderly patients with NSCLC never complete diagnostic and/or staging work-up. Finally, our cohort consists of patients who receive care in the VA system who are predominantly white and male, such that generalizability of our findings to the general population of patients with NSCLC is uncertain. Yet, understanding treatment patterns of veterans with NSCLC is important in its own right, given that the VA is the largest integrated health care system in the United States and a leader in improving health care quality.

In conclusion, despite growing evidence that age and comorbidity together predict prognosis, toxicity, and completion of cancer treatment, age remains a much stronger predictor than comorbidity for the receipt of NSCLC treatment among elderly patients. As NSCLC treatment regimens continue to improve, we will need to address treatment barriers that exist for healthy older adults and also determine ways to reduce the overtreatment of patients with serious comorbidity who are more likely to be harmed by aggressive treatment than to benefit. The ultimate goal is to provide guidelines and tools to encourage individualized treatment decisions that go beyond age and include comorbidity when deciding about appropriate care for the rapidly growing population of older patients with lung cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

AUTHOR CONTRIBUTIONS

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